

Crystal Structure of an Active Two-Domain Derivative of Rous Sarcoma Virus Integrase

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Integration of retroviral cDNA is a necessary step in viral replication. The virally encoded integrase protein and DNA sequences at the ends of the linear viral cDNA are required for this reaction. Previous studies revealed that truncated forms of Rous sarcoma virus integrase containing two of the three protein domains can carry out integration reactions in vitro. Here, we describe the crystal structure at 2.5 Å resolution of a fragment of the integrase of Rous sarcoma virus (residues 49-286) containing both the conserved catalytic domain and a modulatory DNA-binding domain (C domain). The catalytic domains form a symmetric dimer, but the C domains associate asymmetrically with each other and together adopt a canted conformation relative to the catalytic domains. A binding path for the viral cDNA is evident spanning both domain surfaces, allowing modeling of the larger integration complexes that are known to be active in vivo. The modeling suggests that formation of an integrase tetramer (a dimer of dimers) is necessary and sufficient for joining both viral cDNA ends at neighboring sites in the target DNA. The observed asymmetric arrangement of C domains suggests that they could form a rotationally symmetric tetramer that may be important for bridging integrase complexes at each cDNA end.